The relationship of immunologic testing and candidiasis to end-stage renal disease: A review article.

Sundus S. Mahdi[1]* , Thamer A.A. Muhsen[2]

[1,2] Department of Biology, College of Education for Pure Science (Ibn Al-Haitham) college, University of Baghdad, Baghdad, Iraq.

*Correspondence email: sndsamyr3@gmail.com

Received: 16/02/2024
Accepted: 02/05/2024
Online: 20/11/2025

ABSTRACT

Background: This study investigates the relationship between immunological testing, candidiasis, and end-stage kidney disease (ESKD). Individuals with a compromised immune system, such as those with ESKD, are more vulnerable to the fungal infection candidiasis. The study intends to demonstrate the influence of immunological testing on diagnosing and treating candidiasis in the setting of ESKD. **Methodology:** Immunological assays are crucial for identifying *Candida* infections in individuals with ESKD and provide valuable insights into the immune response and vulnerability to fungal pathogens. This research seeks to elucidate the diagnostic and prognostic importance of immunologic markers linked to candidiasis in patients with ESKD. The research investigates the complexities of managing candidiasis in ESKD, including the impact of immunosuppression and renal insufficiency on the immune system. **Results:** The research thoroughly analyzes many literature sources to explore the immunological markers used for diagnosing candidiasis, emphasizing their effectiveness in distinguishing between colonization and invasive fungal infection. The research examines the challenge of treating candidiasis in individuals with ESKD, taking into account the influence of immunosuppressive medications and the need for tailored antifungal approaches. **Conclusions:**The findings of this study might enhance the detection, management, a nd treatment results of candidiasis in patients with ESKD, offering valuable insights to medical professionals, researchers, and healthcare providers caring for these indivi duals.

Keywords: Candidiasis, Immunological Tests, Diagnosis, End-Stage Kidney Disease, Treatment.

https://doi.org/10.24126/jobrc.2025.19.3.828

INTRODUCTION

In the last twenty years, *Candida* species have become one of the primary causes of illness in healthcare institutions, ranking among the top three or four (1). It mainly results in bloodstream infections (BSIs) in preterm newborns and those with catheter-associated *Candida* infection or IV total parenteral nutrition (2;3). *Candida* spp. is fungal species that may reside in the oral cavity as commensal organisms and have a role in the development of severe fungal infections (4).

More than 15 species of *Candida* can cause disease, with *C. glabrata*, *C. tropicalis*, and *C. albicans* being the most prevalent (5). The Pathogenicity of infections and immune system damage varies across animals. The prevalent types of *Candida* infections in the general population are mostly found in the mucous membranes, specifically in the esophagus, oropharynx, and vaginal mucosa. *Candida* infection is quite prevalent in the esophagus, representing up to eighty-eight percent of cases of esophagitis (6).

Kidney failure occurs when the kidneys lose their normal operating capability. The cause of this syndrome may be complex, including diseases, autoimmune disorders, diabetes, different endocrine disorders, cancer, and exposure to toxic chemicals. Chronic kidney disease (CKD) is a prevalent illness that poses a substantial public health problem. Approximately 10-12% of the global population is affected by this condition (7). CKD is a major public health issue with widespread effects on people globally. CKD is defined by the existence of kidney damage or a decreased glomerular filtration rate (GFR), which is regarded as the primary indicator of kidney function. Six

stages of renal problems are linked to the glomerular filtration rate (GFR), with the last stage being known as End-Stage Kidney Disease (ESKD) (8). ESKD is a significant public health concern known for its profound effects on the incidence of diseases and mortality rates. People with ESKD experience a progressive decline in kidney function, leading to the accumulation of waste products and disturbances in fluid and electrolyte balance (9).

Two choices exist for a patient with ESKD who is encountering a life-threatening circumstance. The first choice is to have a kidney transplant, which necessitates locating a compatible kidney donor. The second option is to undergo hemodialysis. Most patients with end-stage kidney disease prefer hemodialysis over kidney transplantation due to reduced surgical risks, avoidance of immunosuppressive medications, and not needing to find a suitable kidney donor (10).

People with ESKD may have immune dysfunction, which increases their vulnerability to infections, including fungal infections such as candidiasis. Immunological tests, such as measuring cytokine levels, studying different types of lymphocytes, and analyzing immunoglobulin patterns, are crucial for evaluating the immune system and infection response in patients with ESKD. Understanding the relationship between these immune variables and candidiasis in patients with end-stage kidney disease is essential for improving patient treatment and outcomes. Several studies have studied the occurrence of *Candida* in the oral cavities of chronic kidney disease patients undergoing hemodialysis and peritoneal dialysis (11). (12) Discovered that *Candida* species' ability to stick to the surface of the mouth may be influenced by diabetes, a weakened immune system, and salivary problems, as well as other systemic illnesses.

Identifying *Candida* in experiments is done using simple methods such as microscopy, culture, or antigen detection assays. Wet mount microscopy is used to identify budding yeast cells as well as hyphal or pseudohyphal types. Additionally, they exhibit robust growth on standard culture media and, when subjected to Gram staining, have a Gram-positive characteristic and an oval form. They utilize multiple verification methods, such as the Vitek 2 structure, which first developed a fluorometric card and subsequently a colorimetric card for the swift recognition of yeast species. Both cards' effectiveness has been assessed through various researches (6;13).

This review, therefore, aims to investigate the correlation between immunological tests, candidiasis, and ESKD in order to provide insights into the diagnostic and prognostic consequences of these relationships.

1. End-Stage Kidney Failure (ESKF)

Chronic renal failure (CRF) is a gradual and permanent deterioration of kidney function caused by the /gradual degeneration of the nephrons over a prolonged period of time. This condition eventually leads to end-stage kidney failure (ESKF), in which the kidneys are no longer able to function adequately. To survive, people with ESKF must undergo long-term renal replacement therapy, such as dialysis, or receive an adequate kidney transplant. Renal failure can result from various pathologies affecting the blood vessels, glomeruli, tubules, and lower urinary tract (14). People with renal insufficiency must ingest between 1800 and 36,000 liters of water per year of dialysis (15). Patients suffering from ESKF often use peritoneal dialysis (PD) as a form of renal replacement treatment in the comfort of their own home (16). The dialysis machine is contaminated with a considerable number of microorganisms, including saprophytic fungi normally found in water and soil. These fungi can behave like parasites (pathogens) in people with a healthy immune system. People receiving hemodialysis suffer from immunosuppression, which makes them particularly susceptible to infections. As a result, they are dependent on regular hospitalizations and surgical interventions, which increase their risk of nosocomial diseases. The most common fungal diseases are those that affect the vascular system (17).

Inadequate personal cleanliness in hemodialysis patients, especially those with a vascular access, increases their susceptibility to infection. It is therefore important to educate these patients on methods to improve and maintain their personal hygiene. Fungal infections at the exit site are more common than peritonitis, but can be treated more quickly. However, they can increase the likelihood of subsequent peritonitis. Fungal infections are usually caused by highly pathogenic fungi, specifically *Candida* species, which cause disease and proliferate either locally or systemically in the human host as a result of a weakened immune system (18).

Bacteria and other microbes thrive in tanks and taps, which are ideal environments for the growth of biofilms. PVC pipes are often used to transport water throughout the water distribution network. This transports microbial

substances via the water to the dialysis machines. Dialysis fluids are inherently non-sterile and susceptible to contamination by various fungi. A variety of saprophytic fungi, including *Cladosporium*, *Fusarium*, *Acremonium*, *Candida parapsilosis*, *Trichoderma*, *Penicillium*, *Verticillium*, *Aspergillus*, and *Chrysosporium*, have been recovered from the water in hemodialysis units (19).

ESRF patients exhibit significant metabolic features, including the accumulation of metabolic waste products and notable changes in biochemical markers such as creatinine clearance (CrCl), urea, and creatinine (Cr). In addition, there are changes in acute-phase proteins such as C-reactive protein (CRP), interleukin-6 (IL-6) (20), albumin, and ferritin, as well as alterations in the lipid profile observed in the plasma of these patients. Severe impairment of renal function, whether sudden or permanent, poses a life-threatening risk and requires the elimination of harmful waste products and the restoration of normal fluid levels and body composition. This can be achieved through the process of dialysis with a synthetic kidney (16; 21; 22; 23; 24).

Inflammation is a natural response of the body to infection, injury, or toxic damage (25). In its acute phase, it can lead to starvation and atherosclerosis. An increase in IL-6 is frequently observed in hemodialysis patients. This increase in IL-6 is thought to be a key factor in the close association between inflammatory processes, stunted growth, and coronary artery disease in hemodialysis patients.

2. Candida Species

The taxonomic classification of the organism is *Candida*, which is a genus of fungi responsible for several diseases in humans and animals. Certain species of *Candida* are benign commensals that inhabit the body of a variety of hosts, particularly humans. However, when the protective boundaries of the host's mucous membranes are compromised or when the immune system is weakened, these species can lead to disease (26). *Candida albicans* is the predominant fungal species responsible for various diseases in humans and animals (Figure 1). It is usually present as a typical part of the microbial community in the gastrointestinal tract of the host, while some species reside as endosymbionts within insect hosts (27).

People undergoing prolonged antibiotic treatment, diabetics, and people with a weakened immune system, including those infected with HIV, have a higher risk of contracting yeast infections (28). *Candida* species can invade a host, either via its own flora or by acquiring the infectious yeast from outside, as several cases stated (29).

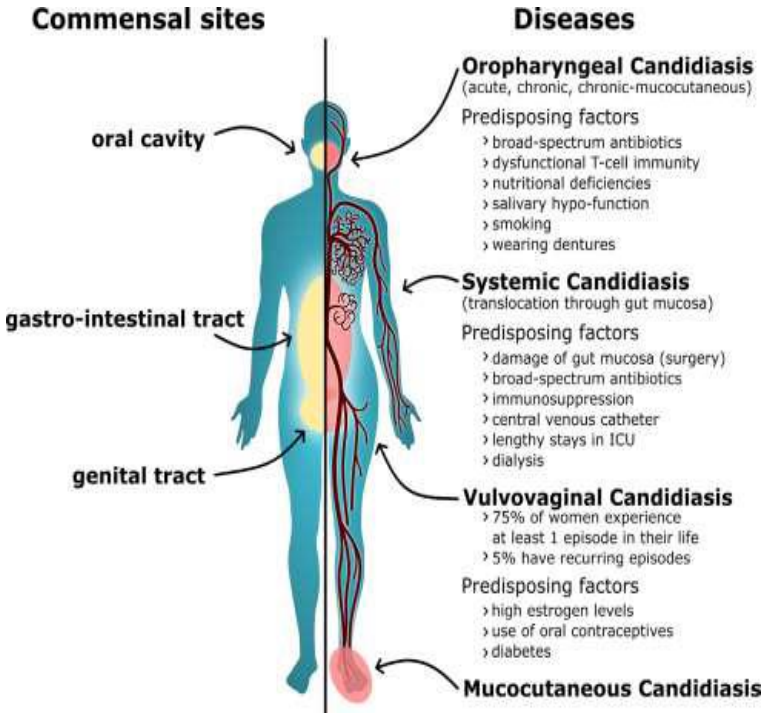

Figure (1): Illness sites on the human body and the commensalism of *Candida albicans* (30).

Candidiasis is a fungal infection caused by *Candida* . According to (31), the infection can be either primary or secondary. The clinical symptoms of candidiasis can range from severe to mild and from chronic to recurrent. Certain *Candida* species are normally present in the human body, but they only grow harmfully under certain circumstances and cause opportunistic infections (32). The primary pathogen is *C. albicans*, but other *Candida* species such as *C. tropicalis*, *C. Krusei*, *C. glabrata*, *C. guillermondii*, and *C. parapsilosis* also contribute to a range of diseases (33). Certain species can cause secondary infections in other species. For example, infection with *C. parapsilosis* can occur as a secondary infection of *C. albicans* in mycotic endocarditis. The incidence of aggressive fungal infection has increased significantly, as previously documented. Several studies have shown that the incidence of disease increases with age (33; 34).

Immunocompromised individuals, including organ and bone marrow transplant recipients, individuals undergoing chemotherapy, and AIDS patients, are at risk for both systemic and disseminated candidiasis (35). Invasive candidiasis is common in patients who have suffered burns, undergone major surgery, received prolonged antibiotic treatment, implanted catheters, or are pregnant, using oral contraception, have diabetes mellitus, suffered local trauma, or are elderly (36).

3. Host immune reactions to Candida spp.

Indoor surroundings are home to a diverse range of fungi, which can cause a variety of ailments in patients with weakened immune systems (37). The innate immune system serves as the first barrier for the host's nonspecific defense against infection. The initial stage of immune system responses involves the interaction between epithelial cells, which play a crucial role in defending the body against attacks by the *C. albicans* pathogen. Many receptors, including mannose receptors (MR), C-type lectin receptors (CLRs), and Toll-like receptors (TLRs), can recognize this pathogen, leading to the release of chemokines and pro-inflammatory cytokines (38).

Phagocytosis, an essential part of the body's defensive system, was among the first mechanisms of innate immunity. Neutrophils, dendritic cells, and macrophages phagocytize *C. albicans* for removal. The cell wall components of *C. albicans*, such as mannan, glucan, and chitin, possess immunostimulatory characteristics that trigger phagocytosis (38). Mannan, also known as the strains that distinguish *Candida* species, is located on the outer surface of the *C. albicans* cell wall (39). Heat-killed *C. albicans* increased the amount of 1,3-glucan normally present in the mannan of the pathogen's cell wall (39).

The process of phagocytosis, in which macrophages engulf glucans, can improve the elimination of pathogens by generating reactive oxygen species (ROS). These ROS are important chemical substances for the elimination of pathogens. However, live *C. albicans* inhibits the production of ROS during the phagocytosis process by phagocytes (40).

Consequently, numerous cells, including epithelial cells, neutrophils, and immunologic cells, produce and manufacture several antimicrobial peptides, such as histatins, LL-37, and β-defensin. LL-37 is a chemotactic substance produced by monocytes and neutrophils. The benefits of suppressing *C. albicans* adherence to plastic surfaces were demonstrated in studies by (41). The β-defensin family, synthesized by epithelial cells, exhibits antibacterial properties against both Gram-negative and Gram-positive bacteria, as well as enveloped viruses, and fungi under laboratory conditions.

Histatins are proteins that are released by the parotid and submandibular glands in human saliva. They have a fungicidal effect against *C. albicans* and may contribute to the formation of tiny membrane defects (38). B and T cells, which are part of the adaptive immune system, have surface receptors that have undergone genetic restructuring. These receptors exhibit a high degree of specificity towards a particular antigen. The innate and adaptive immune responses are closely linked, and an effective adaptive immune response relies on the activation of cells that live in tissues, cells that present antigens, and certain B and T cells. Tissue rebalancing requires a delicate balance between TH17- and TH1-type immune responses and regulatory T cells (Treg cells) (42).

Thus, the activation of CLRs in a living organism leads to the formation of CD4+ T lymphocytes of the TH17 and TH1 types. The TH1 response confers protective immunity against fungi by enhancing the activities of phagocytic cells through the secretion of IFN-γ and facilitating the production of opsonizing antifungal antibodies by B cells. TH17 responses play a critical role in the activation of tissue cells, including epithelial cells and

fibroblasts. This activation leads to the production of chemokines that attract phagocytes to the site of the immune response. The production of the interleukin (IL)-17 families of cytokines, particularly IL-22 and IL-17A, is responsible for this process (43).

Th17 and Th1 cells are the primary T helper subsets that play a critical role in promoting immunity against many pathogenic fungi (44). In addition to the traditional Th1/Th2 responses, Th17 cells have recently been identified as a major subtype of Th cells that provide defense against bacterial and fungal infections that occur outside of cells. Th17 cells primarily generate the cytokine IL-17A, which has several proinflammatory functions such as recruiting neutrophils, enhancing the function of neutrophils and macrophages in phagocytosing foreign substances, and inducing the synthesis of β-defensin (45). IL-17 is recognized as a key component in the immunological reaction to *C. albicans* infection (46).

For a long time, it was thought that cell-mediated immunity (CMI) was an exception, while humoral immunization played a negligible or minimal role in the immune response. It is generally accepted that the CMI mechanism plays a crucial role in defense. However, it is known that only certain types of antibody responses provide protection. In general, Th1-type cell-mediated immunity is desirable to clear a fungal infection, but Th2 immunity often results in susceptibility to invasion (47).

4. Renal Candidiasis.

C. albicans is still the predominant species; however, there is an increase in non-*C. albicans* organisms, particularly *C. tropicalis*, *C. parapsilosis* and *C. glabrata* (48). Candidiasis can lead to considerable illness and death. *Candida* species account for 10 to 15 percent of all hospital-acquired bloodstream infections (49). Invasive candidiasis is often undetectable in healthy individuals. However, there are several well-defined risk factors associated with this particular category of disease. These risk factors include comorbidities such as renal disease and hemodialysis, as well as iatrogenic causes such as chemotherapy or gastrointestinal surgery. There is a strong correlation between burn units and an increased incidence of invasive Candida infections (50).

Systemic candidiasis is a nosocomial infection that occurs in some categories of hospitalized patients who have higher levels of yeast in their mouths and gastrointestinal tract compared to the general population. It is associated with longer hospital stays and a variable risk of death. Patients who are immunosuppressed due to antibiotic or steroid treatment or who have undergone surgical procedures, including organ transplants or heart surgery, are more likely to have a high prevalence of yeasts. *C. albicans* is responsible for eleven percent of all healthcare-acquired urinary tract infections (51).

Renal candidiasis is a disease in which *Candida* spreads through the bloodstream and begins in the gastrointestinal tract. It can develop while a person is undergoing antibiotic or corticosteroid therapy. Lower urinary tract disease is common in women due to local factors (52). Major risk factors for fungal urinary tract infections include the presence of foreign bodies in the urinary system, including stents or stoma tubes, mechanical obstruction of urine flow and renal tubules, impairment of the renal cortex leading to obstruction of the tubules, and hydronephrosis (53). This can lead to pyelonephritis accompanied by secondary fungemia. Renal candidiasis, i.e., pyelonephritis, often results from either an infection that spreads from the top down or, more commonly, from the spread of the *Candida* via the bloodstream from another organ. Symptoms include stiffness, fever, abdominal pain, and discomfort in the lumbar region (54).

Over the last three decades, the number of organ transplants, the spread of the human immunodeficiency virus (HIV), and the increasing use of proven and new immunosuppressive drugs have increased significantly. As a result, the number of people with immunodeficiencies has increased significantly and with it the incidence of invasive fungal infections, which can lead to life-threatening diseases. Clinicians undoubtedly need to improve their knowledge and understanding of clinically significant fungi (54). People suffering from chronic renal failure have disturbances in immune function that affect both the innate and adaptive systems. These consequences include immunosuppression, which increases susceptibility to infections, and stimulation of the immune system, which leads to a persistent inflammatory state (55).

The administration of dialysis therapy may exacerbate some elements of this condition, particularly the triggering of inflammation. In addition, there is an increasing number of people who have resumed dialysis due to rejection of their transplants. A significant number of people have undergone long-term and extensive immunosuppression. These patients are particularly vulnerable (56). Colonization can lead to the development of candidiasis, which can then progress to its more severe form, esophageal candidiasis. If immunosuppression persists or worsens, it also contributes to systemic candidiasis. Renal insufficiency can impair both humoral and cellular immunity by affecting the subsets of T lymphocytes (57). Uremia leads to a reduction in the phagocytic function of macrophages, as shown by (58).

Immunological Tests for *C. albicans* Infection Diagnosis

Immunological approaches include a variety of tools and specific experimental procedures developed by immunologists to stimulate, quantify and characterize immune system responses (59). Immunologists may modify the immune system through cellular, molecular and genetic modification. It is often used for the diagnosis of human diseases. There are a variety of laboratory tests in medical immunology, some of which are necessary for diagnosis and others are helpful in the classification of diseases. Some of them are only relevant for research purposes today, but have the potential to contribute to our collection of tools and knowledge in immunology in the future. Immunological tools are commonly used to diagnose human diseases and are extensively used in clinical and biotechnological settings. These approaches include various methods of immunological analysis (60).

1. Fluorescent Immunoassay

The fluorescence immunoassay is a method for detecting and measuring specific substances using fluorescent markers that bind to target molecules. Immunofluorescence uses antibodies conjugated with fluorescent chemicals known as fluorochromes. Fluorescein isothiocyanate (FITC) is often used as a fluorescent compound in immunology. It attaches to vacant amino groups on proteins. When UV light is focused on FITC, it emits a greenish luminescence. Fluorescence microscopes equipped with UV sources are used to analyze specimens treated with fluorescent antibodies. This test is frequently employed for antigen identification in cells or tissue sections (61). Immunofluorescence is categorized into three main groups.

2. Direct Immunofluorescence

This technique involves detecting the existence of an antigen in medical samples by using a specific antibody labeled with a fluorochrome (62).

3. Indirect Immunofluorescence

This method utilizes two antibodies. The unlabeled primary antibody specifically binds to the targeted molecule. The next antibody, labeled with a fluorophore, subsequently identifies and binds to the original antibody (62).

4. Micro Immunofluorescence

Micro immunofluorescence is a serological technique used to identify antibodies in people' serum (63).

5. Flow cytometry

Flow cytometry is a method that examines and quantifies the properties of individual cells or materials by directing them via a laser beam and identifying the dispersed light or fluorescence produced. Flow cytometry is a technique used to measure cells expressing a specific antigen. The cells are labeled with an antibody that specifically targets the antigen present on their cell surface. The antibody is conjugated with certain fluorescent reagents such as FITC (many other different colored fluorophores are available) and then added to the flow cytometer. The amount of stained cells can be quantified, e.g. the number of CD4+T cells (64).

6. Radioimmunoassay (RIA)

Radioisotopes can be used in radioimmunoassays to determine the level of antibodies or antigens in a serum sample. When measuring antibody levels, a radiolabeled antibody is used to compete with the patient's unlabeled antibody for binding sites on a specific amount of antigen. The main advantage of the radioimmunoassay technique is its high specificity and its ability to detect minute amounts of antigen or antibody. In addition, a large number of experiments can be performed in a very short period of time. The disadvantage lies in the dangers associated with isotopes and the inconsistency (65). However, as Radioimmunoassays (RIAs) became increasingly common,

worries about the increasing amounts of radioactivity generated by research and medical laboratories, and the associated risks to technicians and the environment, also increased (66).

7. Enzyme-linked Immunosorbent Assay (ELISA)

Enzymatic Enzyme-Linked Immunosorbent Assay (ELISA) is a biochemical method used for identifying and quantifying certain molecules, such proteins or antibodies, in a sample. ELISA is a commonly used analytical biochemistry test that was first described by Engvall and Perlmann in 1972. This test was used to measure the presence and amount of antigens or antibodies. ELISA is a very sensitive and simple test used for diagnostic purposes in healthcare, plant pathology, and biotechnology. It is also used as a quality control measure in several industries. Antigens from the sample are attached to the surface of a plate in the simplest form of an ELISA. The antibody is then applied to the surface to form a bond with the antigen. The antibody is linked with an enzyme, and in the last step, a solution containing the enzyme's substrate is added. The following reaction results in a recognizable sign, often appearing as a shift in color (64).

8. Essays about Antibodies

The first nonculture diagnostic techniques were blood tests to detect Candida antigens and anti-Candida antibodies. In Europe, the Mannan and antimannan IgG tests (Platelia Candida Ag-Plus and Ab-Plus Bio-Rad) and *C. albicans* germ tube antibody (CAGTA) assays (Vircell kit and VirClia IgG Monotest) are utilized. However, it is important to note that these tests have not been approved by the Food and Drug Administration (FDA) in the United States (2). In a meta-analysis of 14 trials, the sensitivity and specificity of mannan were found to be 58% and 93%, respectively. Similarly, the sensitivity and specificity of antimannan were 59% and 86%, respectively. The combination mannan/antimannan assay demonstrated a sensitivity of 83% and a specificity of 96%. Patients infected with C. albicans, C. glabrata, and C. tropicalis showed the most favorable results. The meta-analysis revealed substantial variation among the papers included (67).

9. Detection of Beta-D-Glucan (BDG)

BDG is a prevalent polysaccharide that makes up the cell wall of most fungi, except for the Mucorales, *Cryptococc*i, and *Blastomyces dermatitidis*. The Fungitell test, developed by Associates of Cape Cop, Inc. in East Falmouth, MA, USA, is the only assay that has received approval from the FDA. The test is a quantitative, chromogenic immunoassay (EIA) specifically developed to identify BDG by using lysed amebocytes from horseshoe crabs (Lumulis Polyphemus). These cells trigger the process of blood clotting in the presence of BDG in serum samples (68). BDG tests exhibit varying performances due to differences in the B-glucan standards used, specimen preparation techniques, and kit lysates. Multiple meta-analyses have shown that the combined sensitivity and specificity of BDG testing in patients with confirmed or likely invasive fungal infections was 80% (95% confidence interval (CI): 77–82%) and 82% (95% CI: 81–83%), respectively. The highest level of diagnostic accuracy has been reported for a cutoff value more than 80 pg/mL, with an area under the curve (AUC) of 0.92. Alternatively, a cutoff value greater than 60 pg/mL, as defined by the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) EORTC/MSG guidelines, may also be used as the reference standard. The included studies exhibited significant heterogeneity (69).

The primary drawback of this test is the extensive range of factors that can lead to false-positive results, including albumin infusions, human blood products like immunoglobulin, coagulation factors, plasma and protein factors, gauze packing, intravenous amoxicillin-clavulanic acid and piperacillin tazobactam, severe mucositis, enteral nutrition, disruption of the gastrointestinal tract, and systemic bacterial infections. These characteristics are quite common in people who are at risk for candidiasis. Additionally, the limited reusability of 96-well trays restricts the frequency of batch testing because of the increased expense involved.

The accuracy of BDG may be enhanced by identifying successive positive findings. According to Hanson et al., the presence of at least two consecutive positive results yielded a sensitivity of 100%, specificity of 75%, and negative predictive value of 100% for invasive candidiasis in non-neutropenic critically ill patients (70). In a study conducted by Ellis et al., it was shown that individuals with neutropenic fever had a sensitivity of 86.8%, specificity of 81.3%, and negative predictive value of 86.5% (71). Among patients with deep-seated candidiasis but without

candidemia, the sensitivity and specificity of BDG were found to be 56-76.7% and 57-92.9% respectively, according to studies (72,73).

Baseline BDG levels below 416 pg/mL may serve as a reliable indicator of a good prognosis in individuals with IC, with an 89% positive predictive value. Patients who have excellent treatment outcomes often exhibit a negative slope in their B-D glucan levels on serial measures. Conversely, patients who experience treatment failure tend to have a positive slope in their serial measurements (30, 31). Furthermore, BDG has been used as a means of managing antifungal usage, enabling the timely cessation of empirical echinocandin treatment in high-risk ICU patients who consistently test negative (74,75).

10 . The T2-Candida Detection Panel

T2Candida is a diagnostic tool that identifies the presence of Candida in whole blood. It does this by employing an automated system that breaks down blood cells, Candida cells, and detritus by mechanical bead-beating. It then amplifies the DNA using specific primers that target the ribosomal DNA intervening transcribed spacer regions (ITS2) of *Candida* (76). In addition, the amplified PCR product causes the supra-magnetic nanoparticles to clump together, resulting in noticeable alterations in the T2 relaxation time when seen by magnetic resonance. A total of 250 blood culture samples were collected from patients who were sent for the usual standard of care. These samples were manually enriched with clinically significant titers of the 5 *Candida* species that are specifically targeted by T2Candida: *C. albicans*, *C.glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*. The overall sensitivity of the test was 91.1% with a 95% confidence interval (CI) of 86.9–94.2%. The specificity of the test was determined to be 99.4% with a 95% CI of 99.1–99.6%. The detection limits for *C. tropicalis* and *C. krusei* were 1 CFU/mL, for *C. albicans* and *C. glabrata* it was 2 CFU/mL, and for *C. parapsilosis* it was 3 CFU/mL. The average duration for species identification is 4.4 hours with a standard deviation of 1 hour, whereas the blood culture takes an average of 129.9 hours with a standard deviation of 26.3 hours (77).

CONCOLUTIONS

Immunological tests, candidiasis, and ESKD demonstrate the intricate relationship among immune function, fungal infections, and renal health. Immunological tests are crucial for detecting and managing candidiasis in patients with ESKD. These tests enable clinicians to assess immunological reactions, identify fungal infections, and make educated decisions on treatment. The study has outlined the diagnostic and prognostic significance of immunological markers in distinguishing between colonization and invasive fungal infections, offering a crucial insight into the immune status of patients with ESKD.

Furthermore, the challenges of managing candidiasis in patients with end-stage kidney disease have been highlighted, considering the impact of immunosuppression and renal failure on the body's ability to combat fungal infections. The data emphasize the need to create antifungal treatments tailored to target the unique immunological and renal variables in this patient population. Managing candidiasis in end-stage kidney disease requires a multidisciplinary approach including nephrologists, infectious disease specialists, and immunologists, to improve patient care.

References

1. Pappas P.G., Lionakis M.S., Arendrup M.C., Ostrosky-Zeichner L., Kullberg B.J. Invasive candidiasis. Nat. Rev. Dis. Primers, (2018); 4(1): pp. 1-20.
2. Pammi M., Holland L., Butler G., Gacser A., Bliss J.M. *Candida parapsilosis* is a significant neonatal pathogen: a systematic review and meta-analysis. Pediatric Infect. Dis. J., (2013); 32(5): pp. e206.
3. Quindós G. Epidemiology of candidaemia and invasive candidiasis. A changing face. Revista Iberoamericana de Micologia, (2014); 31(1): pp. 42-48.
4. Gulcan A., Gulcan E., Keles M., Aktas E. Oral yeast colonization in peritoneal dialysis and hemodialysis patients and renal transplant recipients. *Compar.* Immunol., Microbiol. Infect. Dis., (2016); 46: pp. 47-52.

5. Pappas P.G., Kauffman C.A., Andes D.R., Clancy C.J., Marr K.A., Ostrosky-Zeichner L., Sobel J.D. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin. Infect. Dis., (2016); 62(4): pp. e1-e50.

6. Shareef S.I., Abdulla A.B.A.S., Saeedi S.M.M. Antifungal Susceptibility of Oral Isolates of Non Albicans *Candida* Species from Chronic Kidney Disease Patients on Hemodialysis. Biochem. Cell. Arch, (2021); 21(2).

7. Levin A., Tonelli M., Bonventre J., Coresh J., Donner J.A., Fogo A.B., Yang C.W. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. The Lancet, (2017); 390(10105): pp. 1888-1917.

8. Alsaedi S.A.M., Al-hashimy A.B.J. The Effect of Bacterial DNA and Hemodialysis Therapy Conditions on Interleukin 6 Levels Variation in End-stage Renal Disease Patients. Int. J. Drug Deliv. Technol., (2022); 12(03): pp.1049-1052.

9. Saleh A.P.M.A.D. Inflammatory role of some cytokines, immunoglobulins and complement proteins in immunopathogenesis of renal failure in a sample of Diyala province patients. Baghdad Sci. J., (2017); 14(2): pp. 0247-0247.

10. Piccoli G.B., Alrukhaimi M., Liu Z.H., Zakharova E., Levin A., World Kidney Day Steering Committee. Women and kidney disease: reflections on World Kidney Day 2018. Clin. Kidney J., (2018); 11(1): pp. 7-11.

11. Godoy J. S., de Souza Bonfim-Mendonça P., Nakamura S.S., Yamada S.S., Shinobu-Mesquita C., Pieralisi N., Svidzinski T.I. Colonization of the oral cavity by yeasts in patients with chronic renal failure undergoing hemodialysis. J. Oral Pathol. Med., (2013); 42(3): pp. 229-234.

12. Yeter H.H., Erten Y., Sevmez H., Korucu B., Kalkanci A., Elbeg S., Yilmaz H. Oral candida colonization as a risk factor for chronic inflammation and atherosclerosis in hemodialysis patients. Therap. Apheresis Dialysis, (2019); 23(6): pp. 542-549.

13. Nerurkar A., Solanky P., Chavda N., Baria H., Desai B. Isolation of Candida Species in clinical specimens and its virulence factor: The biofilm. Int. J. Med. Sci. Public Health, (2012); 1(2): pp. 97-100.

14. Al-Barzinji V.B. Assessment of fungal growth at hemodialysis and peritoneal dialysis unit in Hawler Teaching Hospital. J. Educ. Sci., (2020); 29(2): pp. 279-286.

15. Montanari L.B., Sartori F.G., Cardoso M.J.D.O., Varo S.D., Pires R.H., Leite C.Q.F., Martins C.H.G. Microbiological contamination of a hemodialysis center water distribution system. Revista do Instituto de Medicina Tropical de São Paulo, (2009); 51: pp. 37-43.

16. Wahid H.H.A., Turki K.M., AI-Tharb A.Y. Interleukin-6 Level in serum of Iraqi Patients on Maintenance Hemodialysis Therapy. J. Fac. Med. Baghdad, (2006); 48(4): pp. 431-434.

17. Pires-Gonçalves R.H., Sartori F.G., Montanari L.B., Zaia J.E., Melhem M.S.C., Mendes-Giannini M.J.S., Martins C.H.G. Occurrence of fungi in water used at a haemodialysis centre. Lett. Appl. Microbiol., (2008); 46(5): pp. 542-547.

18. Kleinpeter M.A.Successful treatment of Candida infections in peritoneal dialysis patients: case reports and review of the literature. In Advances in Peritoneal dialysis. Confer. Peritoneal Dialysis, (2004); 20, pp: 58-61.

19. Arvanitidou M., Spaia S., Katsinas C., Pangidis P., Constantinidis T., Katsouyannopoulos V., Vayonas G. Microbiological quality of water and dialysate in all haemodialysis centres of Greece. Nephrol., dialysis, transplantation: Official Public. The Europ. Dialysis Transplant Assoc.-Europ. Renal Assoc., (1998); 13(4): pp. 949-954.

20. Turki S., AL-Naqeeb A., Muhammed Z., Ahmed W.H. Evaluation of Serum Leptin, Interlukein–6 and some Biochemical Parameters in Iraq obese Adult Patients. Medico-Legal Update, (2020); 20(3): pp. 997.

21. Al-Naqqash S., Jawad M.M., Al-Asady Z.T.S., Abdulrazaq S.A. Evaluation of EOS Gene Expression and IL-6 Serum Levels in Iraqi Patients with Psoriasis. Al-Rafidain J. Med. Sci., (2021); 1: pp. 89-93.

22. Hasan T.F., AL-Abassi H.M., Ali H.Z. Cytokines Serum Profile Immunosuppressant Balb/C Mice Infected with Cryptosporidium parvum. Biochemi. Cell. Arch., (2021); 21(2).

23. Jaloud R.E., Hassan F.F., Al-Aamery R.A., Hashim R.T. Histopathological and Immunohistochemical Study of Aflatoxin B1 in Freshly Slaughtered Iraqi Sheep Meat, uses CD Marker of TNF-α. Int. J. Drug Deliv. Technol.,

(2022); 12(2): pp. 798-804.

24. Abed F.A., Mahmood M.A. Evaluation of CRP, IL-6 and Calprotectin in Saliva of Patients Suffering from Crohn's Disease (CD). Ibn AL-Haitham J. Pure Appl. Sci., (2023); 36(4): pp. 102-109.

25. khudhair Hussein D., Al-Jowari S.A.K., Rahmah A.M. Determination of the Level of IL-6 and Vaspin in Hyperthyroid Patients Treated with Carbimazole. Iraqi J. Sci., (2022); 63(5): pp. 1909-1917.

26. Kourkoumpetis T.K., Velmahos G.C., Ziakas P.D., Tampakakis E., Manolakaki D. Coleman J.J., Mylonakis E. The effect of cumulative length of hospital stay on the antifungal resistance of *Candida* strains isolated from critically ill surgical patients. Mycopathologia, (2011); 171: pp. 85-91.

27. Saadaldin, Shama MJ. "A Novel Approach to Overcome Adherence Property of Candida albicans." Al-Nahrain Journal of Science 14.3, (2011): 115-118.

28. AbdAlhussein H. Candidiasis. (Doctoral dissertation, PhD Thesis. Ministry of Higher Education), (2019).

29. Al Bahrani Rusol M., Ali M. Najem, Ibrahim J. Abed. "Variation between Antagonistic Activity of Rosmarinus officinalis Essential Oil and Biosynthesized Silver Nanoparticles from the Essential Oil against Some Fungi." Al-Nahrain Journal of Science 21.4 ,(2018): 61-67.

30. d'Enfert C., Kaune A.K., Alaban L.R., Chakraborty S., Cole N., Delavy M., Brown A.J. The impact of the Fungus-Host-Microbiota interplay upon *Candida albicans* infections: current knowledge and new perspectives. FEMS Microbiol. Rev., (2021); 45(3): pp. 060.

31. Anaissie E.J., McGinnis M.R., Pfaller M.A. Clinical mycology. Ann. Intern. Med., (2003); 138(9): pp. 776.

32. Eloy O., Marque S., Botterel F., Stephan F., Costa J.M., Lasserre V., Bretagne S. Uniform distribution of three *Candida albicans* microsatellite markers in two French ICU populations supports a lack of nosocomial cross-contamination. BMC Infect. Dis., (2006); 6(1): pp. 1-8.

33. Kamiya A., Kikuchi A., Tomita Y., Kanbe T. Epidemiological study of Candida species in cutaneous candidiasis based on PCR using a primer mix specific for the DNA topoisomerase II gene. J. Dermatological Sci., (2005); 37(1): pp. 21-28.

34. Murray P.R., Barron E.J., Pfaller M.A. Mycology on line Candidiasis. Adopted from World Wide Web: http://www. mycology. adelaide. edu. au/myc. 2000.

35. Perlroth J., Choi B., Spellberg B. Nosocomial fungal infections: epidemiology, diagnosis, and treatment. Med. Mycol., (2007); 45(4): pp. 321-346.

36. Richardson M., Lass-Flörl C. Changing epidemiology of systemic fungal infections. Clin. Microbial.Infect., (2008); 14: pp. 5-24.

37. Obaid Wael A. "Assessment of Air Quality Containing Fungi in Al-Nu'man Teaching Hospital." Jornal of Biotechnology Research Center, (2024); 18(1).

38. Kiyoura Y., Tamai R. Innate immunity to *Candida albicans*. Japan. Dental Sci. Rev., (2015); 51(3): pp. 59-64.

39. McKenzie C.G.J., Koser U., Lewis L.E., Bain J.M., Mora-Montes H.M., Barker R.N., Erwig L.P. Contribution of *Candida albicans* cell wall components to recognition by and escape from murine macrophages. Infect. Immun., (2010); 78(4): pp. 1650-1658.

40. Wellington M., Dolan K., Krysan D.J. Live *Candida albicans* suppresses production of reactive oxygen species in phagocytes. Infect. Immun., (2009); 77(1): pp. 405-413.

41. Tsai P.W., Yang C.Y., Chang H.T., Lan C.Y. Human antimicrobial peptide LL-37 inhibits adhesion of *Candida albicans* by interacting with yeast cell-wall carbohydrates. PloS One, (2011); 6(3): pp. e17755.

42. Jolink H., de Boer R., Hombrink P., Jonkers R.E., van Dissel J.T., Falkenburg J.F., Heemskerk M.H. Pulmonary immune responses against Aspergillus fumigatus are characterized by high frequencies of IL-17 producing T-cells. J. Infect., (2017); 74(1): pp. 81-88.

43. Bartemes K.R., Kita H. Innate and adaptive immune responses to fungi in the airway. J. Allergy Clin. Immunol., (2018); 142(2): pp. 353-363.

44. Saijo S., Ikeda S., Yamabe K., Kakuta S., Ishigame H., Akitsu A., Iwakura Y. Dectin-2 recognition of α-mannans and induction of Th17 cell differentiation is essential for host defense against *Candida albicans*. Immunity, (2010); 32(5): pp. 681-691.

45. Brown G.D., Denning D.W., Gow N.A., Levitz S.M., Netea M.G., White T.C. Hidden killers: human fungal infections. Sci. Transl. Med., (2012); 4(165): pp. 165rv13-165rv13.

46. Tomalka J., Ganesan S., Azodi E., Patel K., Majmudar P., Hall B.A., Hise A.G. A novel role for the NLRC4 inflammasome in mucosal defenses against the fungal pathogen *Candida albicans*. PLoS Pathogens, (2011); 7(12): pp. e1002379.

47. Blanco J.L., Garcia M.E. Immune response to fungal infections. Vet. Immunol. Immunopathol., (2008); 125(1-2): pp. 47-70.

48. Nuhair M.N. Incidence of Fungal Infection (*Candida albicans*) in Immuocompramised Patient in Wasit Province (Master dissertation, MScs Thesis. Ministry of Higher Education and Scientific Research. University of Wasit), 2020.

49. Sendid B., Caillot D., Baccouch-Humbert B., Klingspor L., Grandjean M., Bonnin A., Poulain, D. Contribution of the Platelia Candida-specific antibody and antigen tests to early diagnosis of systemic *Candida tropicalis* infection in neutropenic adults. J. Clini. Microbiol., (2003); 41(10): pp. 4551-4558.

50. Brooks G.F., Carroll K.C., Butel J.S., Morse S.A.; Mietzner T.A. Medical Microbiology. Jawetz, Melnick and Adelbergs, (2010).

51. Woldemariam H.K., Geleta D.A., Tulu K.D., Aber N.A., Legese M.H., Fenta G.M., Ali I. Common uropathogens and their antibiotic susceptibility pattern among diabetic patients. BMC Infect. Dis., (2019); 19: pp.1-10.

52. Ellis D. Clinical manifestation of candidiasis. Dsclaimer. (2008); pp: 1-14.

53. Limn C.S.Y., Rosli R., Seow H.F., Chong P.P. *Candida* and invasive candidiasis: back to basics. Europ. J. Clin. Microbial. Infect. Dis., (2012); 31: pp. 21-31.

54. Georgiadou S.P., Kontoyiannis D.P. Fungal infections in primary and acquired immunodeficiencies. Immunogen. Fungal Dis., (2017); 1-34.

55. Imig J.D., Ryan M.J. Immune and inflammatory role in renal disease. Comprehens. Physiol., (2013); 3(2): pp. 957.

56. Kato S., Chmielewski M. Honda H., Pecoits-Filho R., Matsuo S., Yuzawa Y., Lindholm B. Aspects of immune dysfunction in end-stage renal disease. Clin. J. Amer. Soc. Nephrol. CJASN, (2008); 3(5): pp. 1526.

57. Al-Dabagh M.A., Al-Mayah K.S. Evaluation of Immune Response in Patients with Chronic Lymphocytic Leukemia II: Humoral Immune Response. Iraqi J. Sci., (2011); 52(3): pp. 388-393.

58. Vaziri N.D., Pahl M.V., Crum A., Norris K. Effect of uremia on structure and function of immune system. J. Renal Nutrit., (2012); 22(1): pp. 149-156.

59. Van Emon, J.M. (Ed.). Immunoassay and other bioanalytical techniques. CRC Press, (2016).

60. Hassan A.R. New Immunological Technique for Diagnosis of *Candida albicans* Infection (Master dissertation, MScs Thesis. Ministry of Higher Education. Republic of Iraq), (2019).

61. Shoemark A., Frost E. Dixon M., Ollosson S., Kilpin K., Patel M., Hogg C. Accuracy of immunofluorescence in the diagnosis of primary ciliary dyskinesia. Amer. J. Respir. Crit. Care Med., (2017); 196(1): pp. 94-101.

62. Odell I.D., Cook D. Immunofluorescence techniques. J. Investig. Dermatol., (2013); 133(1): pp. e4.

63. Poot A.M., Siland J., Jonkman M.F., Pas H.H., Diercks G.F. Direct and indirect immunofluorescence staining patterns in the diagnosis of paraneoplastic pemphigus. Brit. J. Dermatol., (2016); 174(4): pp. 912-915.

64. Helbert M. Immunology for medical students. Elsevier Health Sciences,(2016).

65. Turgeon M.L. Immunology & Serology in Laboratory Medicine-E-Book. Elsevier Health Sciences, (2020).

66. Alhabbab R.Y., Alhabbab R.Y. Radioimmunoassay (RIA). Basic Serological Testing, (2018): 77-81.

67. Gonzalez-Lara MF, Ostrosky-Zeichner L. Update on the diagnosis of *candidemia* and invasive candidiasis. Current Fungal Infection Reports. (2019) Dec;13: 301-307.

68. Theel ES, Doern CD. Point-counterpoint: β-d-glucan testing is important for diagnosis of invasive fungal infections. Journal of clinical microbiology. (2013) Nov; 51(11): 3478-3483.

69. Onishi A, Sugiyama D, Kogata Y, Saegusa J, Sugimoto T, Kawano S, *et al.* Diagnostic accuracy of serum 1,3-β-D-glucan for Pneumocystis jiroveci pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis. J Clin Microbiol. (2012); 50(1): 7–15.

70. Hanson KE, Pfeiffer CD, Lease ED, Balch AH, Zaas AK, Perfect JR, *et al.* B-D-glucan surveillance with preemptive anidulafungin for invasive candidiasis in intensive care unit patients: a randomized pilot study. PLoS One. (2012); 7(8): 1–8.

71. Ellis M, Al-Ramadi B, Finkelman M, Hedstrom U, Kristensen J, Ali-Zadeh H, *et al.* Assessment of the clinical utility of serial β-D-glucan concentrations in patients with persistent neutropenic fever. J Med Microbiol. (2008); 57(3): 287–295.

72. Fortún J, Meije Y, Buitrago MJ, Gago S, Bernal-Martinez L, Pemán J, *et al.* Clinical validation of a multiplex real-time PCR assay for detection of invasive candidiasis in intensive care unit patients. J Antimicrob Chemother. (2014); 69(11): 3134–3141.

73. Nguyen MH, Wissel MC, Shields RK, Salomoni MA, Hao B, Press EG, *et al.* Performance of candida real-time polymerase chain reaction, β-D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. Clin Infect Dis. (2012); 54(9): 1240–1248.

74. Jaijakul S, Vazquez JA, Swanson RN, Ostrosky-Zeichner L. (1,3)-β-D-glucan as a prognostic marker of treatment response in invasive candidiasis. Clin Infect Dis. (2012); 55(4): 521–526.

75. Sims CR, Jaijakul S, Mohr J, Rodriguez J, Finkelman M, Ostrosky-Zeichner L. Correlation of clinical outcomes with β-glucan levels in patients with invasive candidiasis. J Clin Microbiol. (2012); 50(6): 2104–2106.

76. Neely LA, Audeh M, Phung NA, Min M, Suchocki A, Plourde D, *et al.* T2 magnetic resonance enables nanoparticle-mediated rapid detection of candidemia in whole blood. Sci Transl Med. (2013); 5(182):1–8.

77. Mylonakis E, Clancy CJ, Ostrosky-Zeichner L, Garey KW, Alangaden GJ, Vazquez JA, *et al.* T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis. (2015); 60(6): 892–899.

علاقة الاختبارات المناعية ومرض المبيضات بمرض الكلى في مرحلة الفشل النهائي: المقالة المراجعة

سندس صالح مهدي [1*] ، ثامر عبد الشهيد محسن [2]

[1,2] قسم علوم الحياة / كلية التربية للعلوم الصرفة / ابن الهيثم ، جامعة بغداد ، بغداد ، العراق

الخلاصة

خلفية البحث: تناولت ورقة البحث هذه الارتباط بين الاختبارات المناعية داء المبيضات (كانديدا) ومرض الكلى في مرحلة الفشل النهائي. الأشخاص ذوي الجهاز المناعي المضطرب، مثل أولئك الذين يعانون من مرض الكلى في مرحلة الفشل النهائي، يكونون عرضة بشكل خاص للإصابة بالعدوى الفطرية المعروفة باسم داء المبيضات (الكانديدا). **طريقة العمل:** تهدف هذه الدراسة إلى كشف تداعيات الاختبارات المناعية في تشخيص وإدارة التهاب الكانديدا في سياق. ESKD تعد الاختبارات المناعية ضرورية لاكتشاف العدوى الفطرية بالكانديدا لدى الأشخاص الذين يعانون من ESKD، وتوفر معلومات حيوية حول استجابة الجهاز المناعي وعرضة الجسم للكائنات الفطرية. **الهدف:** تهدف هذا الدراسة إلى توضيح الأهمية التشخيصية والتنبؤية للعلامات المناعية المرتبطة بالتهاب الكانديدا في مرضى ESKD. وعلاوة على ذلك، يستكشف البحث تعقيدات التحكم في التهاب الكانديدا في سياق ESKD، مع مراعاة تأثير التثبيط المناعي والفشل الكلوي على جهاز المناعة في الجسم. **النتائج**: تدرس الدراسة بشكل شامل العديد من المصادر الأدبية للتحقيق في العلامات المناعية المستخدمة في تشخيص التهاب الكانديدا، مع التركيز بشكل خاص على فعاليتها في التمييز بين التعقيم والعدوى الفطرية الغازية. كما تنظر الدراسة في صعوبة علاج التهاب الكانديدا في الأشخاص الذين يعانون من ESKD، مع الأخذ في الاعتبار تأثير الأدوية المثبطة للمناعة وضرورة وجود استراتيجيات مضادة للفطريات مخصصة. يهدف هذا البحث إلى فهم كامل لكيفية قيام الاختبارات المناعية والتهاب الكانديدا وESKD بتسهيل الإصابة بالعدوى الفطرية لدى الأشخاص الذين يعانون بالفعل من مرض الكلى المتقدم. **الاستنتاج:** قد تساهم النتائج التي يتم الحصول عليها من هذه الدراسة في تحسين تحديد الهوية والسيطرة ونتائج العلاج لالتهاب الكانديدا في سياق ESKD، وتوفير توجيهات مفيدة للمهنيين الطبيين والباحثين ومقدمي الرعاية الصحية للمشاركين في علاج هؤلاء المرضى.

الكلمات المفتاحية: داء المبيضات ، الاختبارات المناعية ، التشخيص ، مرض الكلى في مرحلة الفشل النهائي ، العلاج.